1 587 084

PATENT SPECIFICATION (11) 1 587 084

(21) Application No. 35098/77 (22) Filed 22 Aug. 1977
(31) Convention Application Nos. 716 853 and 716 854
(32) Filed 23 Aug. 1976
(31) Convention Application No. 820 521
(32) Filed 1 Aug. 1977 in
(33) United States of America (US)
(44) Complete Specification published 25 March 1981
(51) INT CL³ C07D 333/38; A61K 31/38
(52) Index at acceptance
C2C 1510 1511 20Y 215 220 226 227 22Y 247 254 25Y 29X 29Y 305 30Y 321 32Y 346 351 352 366 367 368 373 37Y 387 401 40Y 455 45X 45Y 464 465 490 552 612 620 625 628 638 658 65X 670 678 719 721 760 771 802 80Y AA LS MV QU TZ

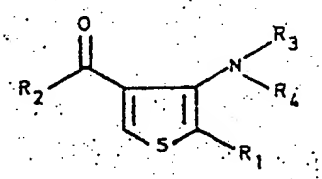
(19)

(54) THIOPHENE DERIVATIVES

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to cyclic compounds. More particularly, the invention is concerned with thiophene derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The thiophene derivatives provided by the present invention are compounds of the general formula



(I)

wherein R_1 represents a lower alkyl, aryl or aralkyl group, R_2 represents a hydrogen atom or a hydroxy, lower alkoxy or amino group and R_3 and R_4, which may be the same or different, each represent a hydrogen atom or a lower alkyl or aralkyl group,
and salts thereof.

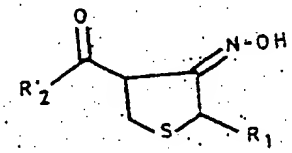
The compounds of formula I and their salts are useful as antiobesity and blood lipid lowering agents. They can also be expected to be useful in the treatment of atherscleröSis and related cardiovascular diseases which are associated with elevated blood lipid levels.

As used in this Specification, the term "lower alkyl", alone or in combination such as in "lower alkoxy" or "aralkyl", denotes a straight-chain or branched-chain saturated aliphatic alkyl group containing from 1 to 8 carbon atoms such as methyl, ethyl, propyl and isopropyl. The term "halogen" includes chlorine, bromine, iodine and fluorine. The term "aryl" denotes mononuclear aryl groups such as phenyl or substituted phenyl, said substitution being in one or more positions and being selected from lower alkyl, trihalomethyl (e.g. trifluoromethyl and trichloromethyl), aralkyl, halogen, lower alkoxy, amino, nitro, mono(lower alkyl)amino and di(lower alkyl)-amino. The term "alkali metal" denotes sodium, potassium or lithium. The term "lower alkanol" denotes an alkanol containing from 1 to 6 carbon atoms The term "alkoxide" refers to a metal salt, preferably an alkali metal or alkaline earth metal salt, of an alkanol. The term "alkaline earth metal" refers to calcium, barium or magnesium. The term "lower alkanoic acid" denotes an alkanoic acid containing from 1 to 8 carbon atoms.

ATTORNEY DOCKET NUMBER:10177-211-999
SERIAL NUMBER: 09/910,388
REFERENCE: B10

Preferred compounds of formula I are those in which R_1 represents a lower alkyl or aryl groups, particularly a lower alkyl group, R_2 represents a lower alkoxy or hydroxy group, particularly a lower alkoxy group, and $-N(R_3)(R_4)$ represents an amino group.

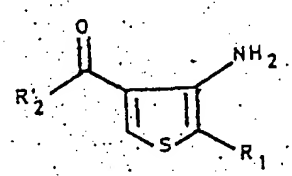
According to the process provided by the present invention, the thiophene derivatives aforesaid (i.e. the compounds of formula I and salts thereof) are manufactured by treating an oxime of the general formula



(II)

wherein R_2' represents a lower alkoxy group and R^1 has the significance given earlier,

with an acid to yield a compound of the general formula



(Ia)

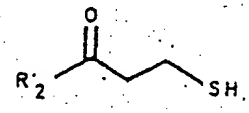
wherein R_2' and R_1 have the significance given earlier,

and, if desired, converting the lower carbalkoxy group into a carboxy, formyl or carbamoyl group and/or reacting the amino group with a lower alkylating or aralkylating agent and, if further desired, converting a compound of formula I into a salt.

A compound of formula Ia can be obtained by treating an oxime of formula II with an acid, preferably a hydrohalide and most preferably hydrogen chloride, in an inert solvent such as an ether, particularly a di(lower alkyl ether (e.g. diethyl ether, a cyclic ether (e.g. tetrahydrofuran or dioxane), a lower alkanol or water. The temperature and pressure at which the treatment is carried out are not critical. The treatment can suitably be carried out at a temperature from about 0°C to 70°C, preferably at room temperature, and at atmospheric pressure.

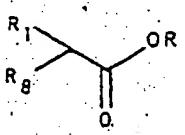
A compound of formula Ia may be converted into a corresponding aldehyde, acid, amide or other ester of formula I or into a salt thereof by conventional methods for converting esters to the aforementioned compounds. Thus, the lower carbalkoxy group contained in a compound of formula Ia can be converted into a carboxy group by basic hydrolysis in a conventional inert organic solvent, preferably a lower alkanol and particularly methanol or ethanol, an aqueous ether solvent, preferably an aqueous di(lower alkyl) ether and particularly diethyl ether, or an aqueous cyclic ether, particularly tetrahydrofuran or dioxane. Among the preferred bases for the basic hydrolysis are the alkali metal hydroxides such as sodium, potassium and lithium hydroxide and the alkaline earth metal hydroxides such as barium, calcium and magnesium hydroxide. The alkali metal hydroxides are especially preferred. The temperature and pressure at which the basic hydrolysis is carried out are not critical. The basic hydrolysis can suitably be carried out at a temperature from about 0°C to 100°C, preferably under reflux and especially at about 70°C, and at atmospheric pressure. By treating a compound of formula Ia with a reducing agent (e.g. lithium aluminium hydride) there is obtained a corresponding primary alcohol which can then be oxidised (e.g. with manganese dioxide) to give a corresponding aldehyde of formula I. By treating a compound of formula Ia with ammonia there is obtained a corresponding amide of formula I in which R_2 represents an amino group. Where a compound of formula I in which R_3 and/or R_4 represents a lower alkyl or aralkyl group is required, these groups may be introduced by conventional procedures for converting an aromatic primary amine to an N-substituted derivative thereof. Thus, a compound of formula Ia can be reacted with a lower alkylating agent (e.g. a lower alkyl halide), an aralkylating agent (e.g. an aralkyl halide) or an alkali metal cyanate (e.g. potassium cyanate).

The oxime starting materials of formula II can be prepared by first reacting a compound of the general formula



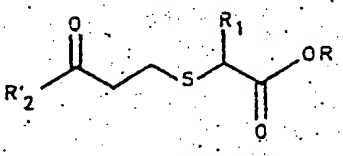
(III)

with a compound of the general formula



(IV)

to form a compound of the general formula

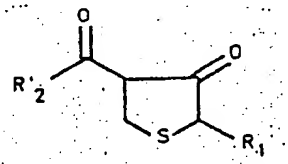


(V)

in which formulae R_1 and R_2' have the significance given earlier, R represents a lower alkyl group and R_3 represents a halogen atom or a mesyloxy or tosyloxy group.

The foregoing reaction can be carried out in the presence of a lower alkanol and an alkali metal alkoxide, preferably methanol and sodium methoxide. Although the temperature and pressure are not critical, the reaction is generally carried out at atmospheric pressure and at a temperature from about 15°C to about 60°C, preferably 25°C.

A compound of formula V is then treated with an alkali metal alkoxide, preferably sodium methoxide, in the presence of an aromatic hydrocarbon, preferably benzene, to form a compound of the general formula



(VI)

wherein R_1 and R_2' have the significance given earlier.

Although the temperature and pressure are not critical, this treatment is generally carried out at atmospheric pressure and at a temperature from about 15°C to about 60°C, preferably 25°C.

A compound of formula VI is then converted into an oxime of formula II using any conventional method for converting a ketone into an oxime. Preferably, a ketone of formula VI is treated with a hydroxylamine hydrohalide, preferably hydroxylamine hydrochloride, in a nitrogen-containing base. Any conventional nitrogen-containing base, preferably an amine, can be used. Among the amines which can be used are primary amines such as lower alkylamines, particularly methylamine and ethylamine, and aniline, secondary amines such as di(lower alkyl)amines, particularly dimethylamine and diethylamine, and pyrrole and tertiary amines such as tri(lower alkyl)amines, particularly trimethylamine and triethylamine, pyridine and picoline. The temperature and pressure are not critical. The treatment can suitably be carried out at a temperature from room temperature to the reflux temperature of the mixture, preferably at about 22°C, and at atmospheric pressure in an inert organic solvent such as an aliphatic or aromatic hydrocarbon (e.g. *n*-hexane or benzene). Preferably, this treatment is carried out using an excess of the nitrogen-containing base which serves as the solvent medium.

The compounds of formulae V and VI in which R_1 represents an aryl or aralkyl group, as well as the oxime starting materials of formula II in which R_1 represents an aryl or aralkyl group, are novel.

The compounds of formula I and their pharmaceutically acceptable salts are effective hypolipemic agents; that is to say, they lower the blood lipid level of mammals. This property has been demonstrated in groups of normal female Charles River rats weighing from 150 to 180 g. They are first fed a corn oil/glucose mixture for several days and then administered the test substances in dimethylsulphoxide (DMSO) either orally or parenterally.

Comparison of the blood triglyceride, fatty acid and cholesterol levels of rats receiving the test substances shows a significant reduction of such levels as compared with the corresponding levels found in untreated animals. Similar results were obtained in the case of the rat hepatocytes.

Fatty acid and cholesterol synthesis in isolated hepatocytes.

Female Charles River rats are fasted for 48 hours and then meal-fed a 1% corn oil/70% glucose diet for 7 to 14 days from 8a.m. to 11 a.m. The isolated rat hepatocytes are prepared by perfusing the liver *in situ*. The hepatocytes are incubated in an oscillating water bath at 37°C for 30 minutes. Each flask contains a volume of 2.1 ml consisting of 1 ml of isolated rat hepatocytes (10—20 mg of dry water cells), 1 ml of Krebs-Henseleit bicarbonate buffer (pH 7.4), 16.5 mmol of glucose, 1 μmol of L-alanine, 1 μCi of [^{14}C]alanine, 1 mCi of ^3H_2O and 2 mmol of inhibitor in water or dimethylsulphoxide at pH 7.4 (unless otherwise specified). All incubations are carried out in triplicate and all experiments are repeated at least twice. Carbon dioxide is collected in each flask after the 60 minutes incubation by adding 0.3 ml of ethanolamine/2-methoxy-ethanol (1:2) to the centre well, 0.4 ml of 62.5% citric acid to the cell media and incubating for 45 minutes. The contents of the centre well are transferred into scintillation counting fluid and $^{14}CO_2$ content is determined. The medium is saponified, acidified (only for determining the rate of lipogenesis) and extracted with hexane. At this stage the lipids are either counted (to determine the rate of lipogenesis) or precipitated with digitonin, washed and counted to determine the rate of chlolesterogenesis). The conversion of ^3H_2O and [^{14}C]alanine into fatty acids or sterols is determined in a liquid scintillation counting system. Results are expressed as nmoles of ^3H_2O and [^{14}C]alanine converted into fatty acids or cholesterol and nmoles of [^{14}C]alanine oxidised to $^{14}CO_2$ per mg of dry weight cells per 60 minutes. The results are set out in Table I hereinafter.

TABLE I

Effect of 3-Amino-4-Carbomethoxy-2-*n*-Propylthiophene Hydrochloride on Lipid Synthesis and CO_2 Production in Isolated Rat Hepatocytes[a]

Treatment	Dose	Fatty Acid Synthesis		Cholesterol Synthesis		CO_2 Production
	nmol	^3H_2O	[^{14}C]alanine converted	^3H_2O converted	[^{14}C]alanine	[^{14}C]alanine converted
		As % of Control				
Control (DMSO)	–	100	100	100	100	100
3-Amino-4-carbomethoxy-2-*n*-propylthiophene hydrochloride	0.05	17*	9*	28*	19*	49*
	0.25	21*	10*	29*	21*	50*
	0.10	18*	10*	35*	23*	53*
	0.05	18*	11*	33*	26*	54*
	0.01	30*	19*	49*	31*	73*

[a]Each flask contained 13.7 mg of cells dry weight and 25 µl of dimethylsulphoxide. Each value is the mean of 2 to 14 determinations.

*Statistically different from control value.

Fatty acid and cholesterol synthesis *in vivo*.

Rats are prepared by fasting for 48 hours and re-feeding a 1%corn oil/70% glucose diet for 5 to 15 days. On the day of the experiment, the rats are dosed 30 minutes before the 3 hour meal by oral intubation or after the end of the 3 hour meal by intraperitoneal injection. Rats are killed by decapitation after a 30 minute pulse consisting of 1 mCi of ^3H_2O, µCi of [^{14}C]alanine, 12.3 mg of alanine and 30.6 mg of α-ketoglutaric acid in 0.25 ml of saline given at the end of the 3 hour meal by intravenous injection into the tail vein. The livers are quickly excised, saponified and acidified (only for determining the rate of lipogenesis) and extracted with hexane. At this stage the lipids are either counted (to determine the rate of lipogenesis) or precipitated with digitonin, washed and counted (to determine the

rate of cholesterogenesis). The conversion of ^3H_2O and [^{14}C]alanine into fatty acids or sterols is determined in a liquid scintillation counting system. The results are set out in Tables II—V hereinafter.

TABLE II.

Effect of Intraperitoneal Administration of 3-Amino-4-Carbomethoxy-2-*n*-Propylthiophene Hydrochloride on *In Vivo* Lipogenesis and Cholesterogenesis

	Dose	Fatty Acid Synthesis[a]	Cholesterol Synthesis[a]	
	mmoles/kg	nmoles of [^{14}C]alanine converted/g/30 min.	μmoles of ^3H_2O converted/g/30 min.	nmoles of [^{14}C]alanine converted/g/30 min.
Control (1% gum arabic)	—	614 ± 66	1.36 ± 0.07	35.7 ± 3.2
3-Amino-4-carbomethoxy-2-n-propylthiophene hydrochloride	0.1	251 ± 36*	0.85 ± 0.06**	17.6 ± 1.9

[a]Results are expressed as μmoles of ^3H_2O and nmoles of [^{14}C]alanine converted into fatty acids or cholesterol per gram of liver per 30 minutes.

*p >0.01 **p >0.001.

1,587,084

TABLE III

Effect of 3-Amino-4-Carbomethoxy-2-*n*-Propylthiophene Hydrochloride on Serum Lipids.

	Administration route	Dose mmoles/kg	Tri-glycerides mg %	Cholesterol mg %
Control (%) gum arabic:	i.p.	—	67 ± 4	116 ± 7
3-Amino-4-carbomethoxy-2-*n*-propyl-thiophene hydrochloride	i.p.	0.1	51 ± 3*	105 ± 11

*p>0.01.

TABLE IV

Effect of Oral Administration of 3-Amino-4-Carbomethoxy-2-*n*-Propylthiophene Hydrochloride on *In Vivo* Fatty Acid Synthesis

	Dose	Fatty Acid Synthesis [a]			
	mmoles/kg	μmoles of ^3H_2O converted/g/30 min.	% of Control	nmoles of [^{14}C]alanine converted/g/30 min.	% of Control
Control (1% gum arabic)	—	19.6 ± 2.4	100	473 ± 76	100
3-Amino-4-carbo-methoxy-2-*n*-propylthiophene hydrochloride	1.2	7.1 ± 1.7*	36	162 ± 60*	34

[a]Results are expressed as μmoles of ^3H_2O and nmoles of [^{14}C]alanine converted into fatty acids per gram of liver per 30 minutes.

*p >0.01.

TABLE V

Effect of Oral Administration of 3-Amino-4-Carbomethoxy-2-*n*-Propylthiophene Hydrochloride on Cholestorogenesis

	Dose nmoles/kg	μmoles of ^3H_2O[a] converted/g/30 min.	% of Control	nmoles of [^{14}C]alanine[a] converted/g/30 min.	% of Control
Control (1% gum arabic)	—	1.35 ± 0.04	100	33.0 ± 3.1	100
3-Amino-4-carbomethoxy-2-*n*-propylthiophene hydrochloride	1.2	0.88 ± 0.16*	65	15.2 ± 3.2**	46
	0.4	0.96 ± 0.05***	71	17.4 ± 0.9***	53

[a]Results are expressed as μmoles of ^3H_2O and nmoles of [^{14}C]alanine converted into cholesterol per gram of liver per 30 minutes.

*p >0.05 **p >0.01 ***p >0.001

The compounds of formula I and the pharmaceutically acceptable salts thereof can be administered parenterally as well as orally. For parenteral administration, solutions and suspension of said compounds in dimethylsulphoxide, water or gum arabic can be used. Of particular suitability are sterile aqueous solutions of the corresponding water-soluble salts. These dosage forms are especially suitable for peritoneal injection. The aqueous solutions, including those of the salts, dissolved in pure distilled water, are also useful for intravenous injection purposes provided that their pH is properly adjusted prior to such injection. Such solutions should also be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. In this connection, the sterile aqueous media used are readily obtained by standard and well-known techniques. For example, distilled water is ordinarily used as the liquid diluent.

The dosage required to lower the blood lipid level will be determined by the nature and the extent of the symptoms. Generally, small dosages will be administered initially with a gradual increase in dosage until the optimum level is determined. It will generally be found that when a pharmaceutical preparation provided by this invention is administered orally, larger quantities of the active ingredient will be required to produce the same level as produced by a smaller quantity administered parenterally. In general, from about 0.1 to 1.2 mg of active ingredient per kilogram of body weight administered in single or multiple dosage units significantly lowers the blood lipid level.

1,587,084

It will be appreciated that the present invention also includes within its scope a pharmaceutical preparation containing a compound of formula I hereinbefore or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier material.

The following Examples illustrate the process provided by the present invention.

Example 1.

Gaseous hydrogen chloride was bubbled into 1 litre of anhydrous diethyl ether in which 100.0 g of 4 - carbomethoxy - 3 - keto - 2 - *n* - propyltetrahydrothiophene oxime had been dissolved. This procedure was carried out at 0°C for 1 hour. The reaction flask was stoppered with a drying tube and the contents were stirred at room temperature overnight. The solvent was evaporated until the product crystallised. The white solid was collected by filtration and washed well with diethyl ether to yield 60.0 g of 3 - amino - 4 - carbomethoxy - 2 - *n* - propylthiophene hydrochloride of melting point 178°—180°C. The product was recrystallised from methanol/diethyl ether to yield 50.0 g of pure 3 - amino - 4 - carbomethoxy - 2 - *n* - propylthiopthene hydrochloride of melting point 180°—181°C.

The starting material can be prepared as follows:

a) A solution of 116.55 g of methyl 3-mercaptopropionate in 220 ml of dry methanol at – 20°C was treated with 52.46 g of sodium methoxide. After 20 minutes, a solution of 203.0 g of ethyl 2-bromovalerate in 150 g of dry methanol was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The methanol was evaporated and the residue partitioned between diethyl ether and water. The organic phase was washed with 10% bicarbonate solution and water. After drying over magnesium sulphate, the diethyl ether was evaporated to yield 130 g of methyl 4 - thia - 5 - carbomethoxyoctanoate as a colourless oil.

b) To a suspension of 54.0 g of sodium methoxide in 500 ml of anhydrous benzene were added dropwise at 25°C 130 g of methyl 4 - thia - 5 - carbomethoxyoctanoate. The mixture was stirred overnight and poured into ice-water. The aqueous phase was extracted with benzene/diethyl ether (1:1) and then acidified to pH 1 with 6-*N* hydrochloric acid. The product, which partially separated from the water at this point, was taken up in methylene chloride. The aqueous layer was further extracted with methylene chloride. The combined organic phases were dried and evaporated to yield 94.0 g of pure 4 - carbomethoxy - 3 - keto - 2 - *n* - propyltetrahydrothiophene as a colourless oil.

c) A solution of 94.0 g of 4 - carbomethoxy - 3 - keto - 2 - *n* - propyltetrahydrothiophen in 250 ml of dry pyridine was treated with 40.0 g of hydroxylamine hydrochloride at 25°C. the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue partitioned between 1-*N* hydrochloric acid and methylene chloride. The organic phase was dried over sodium sulphate and evaporated to yield 100 g of pure 4 - carbomethoxy - 3 - keto - 2 - *n* - propyltetrahydrothiophene oxime as a colourless oil.

Example 2.

A solution of 41.1 g of 4 - carbomethoxy - 3 - keto - 2 - methyltetrahydrothiophene oxime in 600 ml of anhydrous diethyl ether, previously saturated with gaseous hydrogen chloride at 0°C, was left to stir at 25°C overnight. The separated solid was collected, washed well with diethyl ether and dried to yield 33.2 g. Evaporation of the filtrate yielded, after recrystallisation of the residue, an additional 4.2 g; the total yield of pure 3 - amino - 4 - carbomethoxy - 2 - methylthiophene hydrochloride being 37.4 g. This compound melted at 191°—192°C.

In a similar manner, 49.12 g of 4 - carbomethoxy - 2 - *iso*propyl - 3 - ketotetrahydrothiophene oxime were converted into 18.49 g of 3 - amino - 4 - carbomethoxy-2 - *iso*propylthiophene hydrochloride of melting point 185°C (decomposition).

The starting material can be prepared as follows:

a) A solution of 66.29 g of methyl 3-mercaptopropionate in 50 ml of anhydrous methanol was cooled to 0°C and treated with 120 ml of a 25% solution of sodium methoxide in methanol. To this solution were added dropwise 100 g of ethyl 2-bromopropionate in 100 ml of anhydrous methanol. The reaction was allowed to proceed at 25°C overnight. The solvent was evaporated and the residue partitioned between diethyl ether and 10% sodium bicarbonate. The aqueous phase was further extracted with diethyl ether. The combined organic extracts were dried over magnesium sulphate and evaporated to yield 121.40 g of 2 - methyl - 3 - thia - 1,6 - hexanedioc acid - 1-

ethyl - 6 - methyl ester as a pale yellow oil.

In a similar manner, 61.4 g of methyl 3-mercaptopropionate were reacted with 106.8 g of ethyl 2-bromovalerate to yield 120.91 g of 2 - *iso*propyl - 3 - thia - 1,6-hexanedionic acid - 1 - ethyl - 6 - methyl ester.

b) A solution of 121.4 g of 2 - methyl - 3 - thia - 1,6 - hexanedionic acid - 1-ethyl - 6 - methyl ester in 90 ml of dry benzene was added dropwise to a suspension of 30 g of anhydrous sodium methoxide in 200 ml of dry benzene. The reaction was allowed to proceed to room temperature overnight. The mixture was partitioned between water and diethyl ether. The aqueous phase was further extracted with benzene. The aqueous phase was then acidified to pH 1 with 6-*N* hydrochloric acid and extracted three times with methylene chloride. The methylene chloride extracts were combined, dried over sodium sulphate and evaporated to yield 79.17 g of pure 4 - carbomethoxy-3 - keto - 2 - methyltetrahydrothiophene as a colourless oil.

In a similar manner, 120.91 g of 2 - *iso*propyl - 3 - thia - 1,6 - hexanedionic acid-1 - ethyl - 6 - methyl ester were converted into 91.0 g of 4 - carbomethoxy - 2-*iso*propyl - 3 - ketotetrahydrothiophene.

c) A solution of 37.26 g of 4 - carbomethoxy - 3 - keto - 2 - methyltetrahydrothiophene in 100 ml of anhydrous pyridine was treated with 18.0 g of hydroxylamine hydrochloride. The mixture was stirred for 24 hours at 25°C. The mixture was centrated and partitioned between 1-*N* hydrochloric acid and methylene chloride. The aqueous phase was extracted twice with methylene chloride. The aqueous phase was extracted twice with methylene chloride. The combined organic extracts were dried and evaporated to yield 40.1 g of pure 4 - carbomethoxy - 3 - keto - 2 - methyltetrahydrotheophene oxime as a colourless oil..

In a similar manner, 52.8 g of 4 - carbomethoxy - 2 - *iso*propyl - 3 - keto-tetrahydrothiophene were converted into 49.0 g of 4 - carbomethoxy - 2 - *iso*propyl-3 - ketotetrahydrothiophene oxime.

Example 3.

A solution of 2.07 g of 3 - amino - 4 - carbomethoxy - 2 - methylthiophene hydrochloride in 35 ml of methanol was treated with 23 ml of 1-*N* sodium hydroxide. The mixture was heated under reflux for 0.5 hour, cooled and poured into brine. The pH was adjusted to 5 and extracted seven times with methylene chloride/methanol (4:1). The organic extracts were combined, dried and evaporated to yield 1.23 g of pure 3 - amino - 4 - carboxy - 2 - methylthiophene of melting point 162°—164°C. This compound was recrystallised from ethyl acetate/pentane to yield an analytical sample of melting point 163°—164°C.

In a similar manner, 5.0 g of 3 - amino - 4 - carbomethoxy - 2 - *iso*propyl-thiophene hydrochloride were converted into 3.3 g of 3 - amino - 4 - carboxy - 2-*iso*propylthiophene of melting point 117°—118°C.

Also in a similar manner, 1.41 g of 3 - amino - 4 - carbomethoxy - 2 - *n* - propyl-thiophene hydrochloride were converted into 0.625 g of 3 - amino - 4 - carboxy-2 - *n* - propylthiophene of melting point 144°—145°C.

Example 4.

Gaseous hydrogen chloride was bubbled at 0°C for 1 hour into a solution of 80.0 g of 4 - carbomethoxy - 3 - keto - 2 - phenyltetrahydrothiophene oxide in 600 ml of anhydrous diethyl ether. The suspension was treated with 300 ml of methanol and stirred at 25°C overnight. The product was collected by filtration and washed with diethyl ether to yield 70.0 g of 4 - amino - 5 - phenylthiophene - 3 - carboxylic acid methyl ester hydrochloride as a pale yellow solid of melting point 181°—182°C. This compound may be recrystallised from methanol.

The starting material can be prepared as follows:

a) A solution of 104.95 g of methyl 3-mercaptopropionate in 200 ml of methanol was cooled to 0°C and treated with 207.5 g of a 25% solution of sodium methoxide in methanol. To the resulting homogeneous solution were added dropwise under argon 200.0 g of methyl α-bromo-phenyl acetate in 200 ml of methanol. The mixture was stirred at 25°C overnight. The solvent was removed by evaporation and the residue partitioned between water and methylene chloride to yield 234.0 g of 2-phenyl - 3 - thia - adipic acid dimethyl ester as a colourless oil.

b) A solution of 234.0 g of 2 -phenyl - 3 - thia - adipic acid dimethyl ester in 300 ml of dry benzene was added dropwise at 25°C to 54.05 g of sodium methoxide.

The mixture was stirred overnight and poured into water. The solid was filtered off and the filtrate extracted twice with diethyl ether. The solid was then added to the aqueous phase which was acidified to pH 1 with 6-*N* hydrochloric acid. The mixture was extracted three times with methylene chloride. The organic extracts were dried over sodium sulphate and evaporated to yield 145.24 g of 4 - carbomethoxy - 3-keto - 2 - phenyltetrahydrothiophene as a pale yellow oil.

c) A solution of 82.24 g of 4 - carbomethoxy - 3 - keto - 2 - phenyltetrahydrothiophene in 120 ml of anhydrous pyridine was treated with 28.85 g of hydroxylamine hydrochloride. The solution was stirred at 25°C for 2 days and the solvent then evaporated *in vacuo*. The residue was partitioned between 1-*N* hydrochloric acid and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined, dried over sodium sulphate and evaporated to yield 90.0 g of 4 - carbomethoxy - 3 - keto - 2 - phenyltetrahydrothiophene oxime as a colourless oil.

Example 5.

A solution of 10.0 g of 4 - amino - 5 - phenylthiophene - 3 - carboxylic acid methyl ester hydrochloride in 80 ml of methanol was treated with 82 ml of 1-*N* sodium hydroxide. The mixture was heated under reflux for 0.5 hour and then cooled to room temperature. The pH was adjusted to 5 and the product which separated was filtered off and dried to yield 8.2 g of pure 4 - amino - 5 - phenylthiophene-3 - carboxylic acid of melting point 201°—202°C after recrystallisation from ethyl acetate/pentane.

Example 6.

Preparation of 4 -amino - 5 - ethyl - 3 - thiophenecarboxylic acid methyl ester hydrochloride.

To a solution of 125 g of methyl 3-mercaptopropionate in 75 ml of dry methanol were added dropwise at 0°C 249 ml of 25% sodium methoxide/methanol. The resulting mixture was treated dropwise at 0°C with 200 g of ethyl 2-bromobutyrate in 75 ml of dry methanol. The cooling bath was removed and the mixture stirred overnight at 25°C. The mixture was concentrated and partitioned between water and methylene chloride. The organic extracts were dried and evaporated to yield 229 g of diester as a colourless oil.

To a suspension of 63.5 g of sodium methoxide in 300 ml of dry benzene were added dropwise at 25°C 229 g of the foregoing diester in 200 ml of dry benzene. After stirring overnight at room temperature, the mixture was poured into 800 ml of water and the benzene layer was further extracted with 200 ml of water. The aqueous phases were combined, carefully acidified with 6-*N* hydrochloric acid and extracted three times with methylene chloride/methanol (5:1). The organic extracts were dried and evaporated to yield 149.7 g of pure ketone as a colourless oil.

To a solution of 276.1 g of the foregoing ketone in 500 ml of anhydrous pyridine were added in several portions 121.6 g of hydroxylamine hydrochloride. The reaction was allowed to proceed for 20 hours at 25°C, the mixture was concentrated and partitioned between methylene chloride and 3-*N* hydrochloric acid. The aqueous phase was back-washed twice with methylene chloride/methanol (5:1). The organic phases were dried and evaporated to yield 253 g (82%) of pure oxime as a pale yellow oil.

A solution of 253 g of the foregoing oxime in 2 litres of anhydrous diethyl ether was treated at 25°C with a stream of gaseous hydrogen chloride for 1 hour. The mixture was seeded with 0.5 g of authentic product and stirred overnight at 25°C. The crude product was filtered off, washed with anhydrous diethyl ether and recrystallised from methanol/diethyl ether to yield 173 g of the desired pure aminothiophene hydrochloride of melting point 161°C.

The following Examples illustrate pharmaceutical preparations containing 3-amino - 4 - carbomethoxy - 2 - *n* - propylthiophene hydrochloride as the active ingredient:

Example A

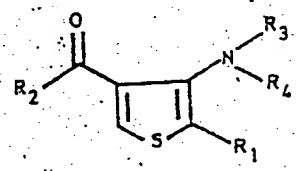
Capsule Formulation	Per capsule	
Active ingredient	10 mg	50 mg
Lactose	10 mg	125 mg
Corn starch	30 mg	30 mg
Talc	5 mg	5 mg
Total weight	210 mg	210 mg

Example B:

Tablet Formulation	Per tablet
Active ingredient	25.00 mg
Dicalcium phosphate dihydrate unmilled	175.00 mg
Corn starch	24.00 mg
Magnesium stearate	1.00 mg
Total weight	225.00 mg

WHAT WE CLAIM IS:—

1. Compounds of the formula



(I)

wherein R_1 represents a lower alkyl, aryl or aralkyl group, R_2 represents a hydrogen atom or a hydroxy, lower alkoxy or amino group and R_3 and R_4, which may be the same or different, each represent a hydrogen atom or a lower alkyl or aralkyl group,
and salts thereof.

2. A compound of formula I given in claim 1, wherein R_1 represents a lower alkyl or aryl group, R_2 represents a lower alkoxy or hydroxy group and $—N(R_3)(R_4)$ represents an amino group, and salts thereof.

3. A compound according to claim 2, wherein R_1 represents a lower alkyl group, R_2 represents a lower alkoxy group and $—N(R_3)(R_4)$ represents an amino group, and salts thereof.

4. 4 - Amino - 5 - ethyl - 3 - thiophenecarboxylic acid methyl ester hydrochloride.

5. 3 - Amino - 4 - carbomethoxy - 2 - *n* - propylthiophene hydrochloride.

6. 3 - Amino - 4 - carboxy - 2 - methylthiophene.

7. 3 - Amino - 4 - carbomethoxy - 2 - methylthiophene hydrochloride.

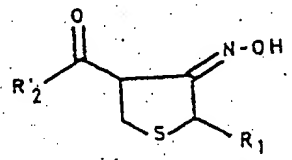
8. 3 - Amino - 4 - carboxy - 2 - *iso*propylthiophene.

9. 3 - Amino - 4 - carbomethoxy - 2 - *iso*propylthiophene hydrochloride.

10. 4 - Amino - 5 - phenylthiophene - 3 - carboxylic acid methyl ester hydrochloride.

11. 4 - Amino - 5 - phenylthiophene - 3 - carboxylic acid.

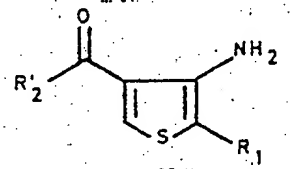
12. A process for the manufacture of the thiophene derivatives claimed in claim 1, which process comprises reacting an oxime of the general formula



(II)

wherein R_2' represents a lower alkoxy group, and R_1 has the significance given in claim 1,

with an acid to yield a compound of the general formula



(Ia)

wherein R_2' has the significance given earlier in this claim and R_1 has the significance given in claim 1,

and, if desired, converting the lower carbalkoxy group into a carboxy, formyl or carbamoyl group and/or reacting the amino group with a lower alkylating or aralkylating agent and, if further desired, converting a compound of formula I into a salt.

13. A process according to claim 12, wherein there is manufactured a compound of formula I in which R_1 represents a lower alkyl or aryl group, R_2 represents a lower alkoxy or hydroxy group and $-N(R_3)(R_4)$ represents an amino group, or a salt thereof.

14. A process according to claim 13, wherein there is manufactured a compound of formula I in which R_1 represents a lower alkyl group, R_2 represents a lower alkoxy group and $-N(R_3)(R_4)$ represents an amino group, or a salt thereof.

15. A process according to claim 12, wherein 4 - amino - 5 - ethyl - 3-thiophenecarboxylic acid methyl ester hydrochloride is manufactured.

16. A process according to claim 12, wherein 3 - amino - 4 - carbomethoxy-2 - *n* - propylthophene hydrochloride is manufactured.

17. A process for the manufacture of the thiophene derivatives claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples 1 to 6.

18. A thiophene derivative as set forth in claim 1, when manufactured by the process claimed in any one of claims 12 to 17 inclusive or by an obvious chemical equivalent thereof.

19. A pharmaceutical preparation containing a compound of formula I given in claim I or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier material.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43, Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☒ OTHER: small text

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.